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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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EXAMINER

KAM, CHIH MIN

ART UNIT PAPER NUMBER

1656

DATE MAILED: 08/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | | |
|------------------------------|--------------------------------------|---|--|
| Office Action Summary | Application No. 09/742,008 | Applicant(s) VISOV, CHRISTIAN | |
| | Examiner Chih-Min Kam | Art Unit 1656 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 June 2006.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,5-13,15-21,23 and 24 is/are pending in the application.
- 4a) Of the above claim(s) 15-21 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,5-13,23 and 24 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of the Claims

1. Claims 1, 5-13, 15-21, 23 and 24 are pending.

Applicants' amendment filed June 2, 2006 is acknowledged. Applicants' response has been fully considered. Claims 1 and 13 have been amended, and claims 3, 4 and 14 have been cancelled. Claims 15-21 are non-elected invention and withdrawn from consideration. Therefore, claims 1, 5-13, 23 and 24 and are examined.

Withdrawn Claim Objections

2. The previous objection to claims 4 and 23 is withdrawn in view of applicants' amendment to the claim, applicants' cancellation of the claim, and applicant's response at page 12 of the amendment filed June 2, 2006.

Withdrawn Claim Rejections - 35 USC § 112

3. The previous rejection of claims 1, 3, 5-13 and 24, under 35 U.S.C. 112, first paragraph, is withdrawn in view of applicants' amendment to the claim, applicants' cancellation of the claim, and applicants' response at pages 9-11 in the amendment filed June 2, 2006.
4. The previous rejection of claims 14, under 35 U.S.C. 112, second paragraph, is withdrawn in view of applicants' cancellation of the claim in the amendment filed June 2, 2006.

New Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1 and 5-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 5-12 are indefinite because the claims lack an essential step in the method of preparing a polyanion of cyclosporin. The omitted step is the outcome of the process, it is not clear whether the polyanion is obtained or not. Claims 5-12 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

New Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

3. Claims 13, 23 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barriere *et al.* (U. S. Patent 5,994,299, filed December 23, 1997) in view of Seebach *et al.* (Helvetica Chimica Acta 76, 1564-1590 (1993)) and Gordon *et al.* (U. S. Patent 5, 559,256, published on September 24, 1996).

Barriere *et al.* disclose preparation of [4'-hydroxy-MeLeu]⁴-cyclosporin compounds of general formula (I) by treating the cyclosporine of formula (II) (having Sar at position 3) with a lithium derivative such as n-butyllithium, lithium diisopropylamide or a mixture to activate sarcosine at the 3-position; and then reacting with a disulfide (i.e., R-Alk-S-S-Alk-R), where the

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group at 3-position is -S-Alk-R, and Alk and R are each defined (e.g., the -S-Alk-R group can be (R)-2-(N,N-dimethylamino)ethylthio; Example 1; claim 23), and where the hydroxyl radicals that interfere with the reaction can be protected before the treatment and the protecting group can be removed after the treatment (column 1, lines 49-65; column 3, line 62- column 4, line 60; claim 24). However, Barriere *et al.* do not teach the use of a hexamethyldisilazane metal salt to activate the cyclosporine of formula (II) to form a polyanion.

Seebach *et al.* disclose an enolate of cyclosporine A including sarcosine enolate can be formed when cyclosporine A is treated with lithium diisopropylamide (LDA), where the deprotonation at sarcosine occurs, and the alkylation product can be detected after reacting with an alkylating agent (page 1565; Schemes 1 and 2; Table at page 1566); and Gorden *et al.* disclose the protected amino ester LXVIII can be alkylated via its enolate anion, which is formed by treatment of the ester with a base such as lithiumdisoporpylamide, lithium bis(trimethylsilyl)amide (another name for hexamthyldisilazane lithium salt, see attached STN search result) or the like to give LXIX (columns 43-44; column 47, lines 29-35).

At the time of invention was made, it would have been obvious that one of ordinary skill in the art is motivated to combine the three references to prepare a [4'-hydroxy-MeLeu]⁴-cyclosporin compound of general formula (I) via a polyanion intermediate as indicated by Barriere *et al.* using either hexamethyldisilazane lithium salt or lithiumdisoporpylamide to make the cyclosporine polyanion intermediate (claim 13) because both reagents are strong base and can deprotonate the sarcosine present on the cyclosporin to form an enolate anion, which is then reacting with an alkylating agent to form a cyclosporine derivative. Thus, the combined

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references result in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

Conclusion

7. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4.30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
Primary Patent Examiner



primary **CHIH-MIN KAM**
PATENT EXAMINER

CMK

August 12, 2006